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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,808	11/14/2003	Dave S.B. Hoon	JWCI 0035 PUSP	4483

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EXAMINER	
AEDER, SEAN E	

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10,34-38 and 40-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 10, 34-38, and 40-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/23/10 has been entered.

Claims 41-47 have been added by Applicant.

Claims 1-5, 7, 10, 34-38, and 40-47 are pending.

Claims 1-3, 7, 35, 36, and 40 have been amended by Applicant.

Claims 1-5, 7, 10, 34-38, and 40-47 are currently under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 10, 34-36, 38, and 40 remain rejected, and claims 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826) for the reasons stated in the Office Action of 11/4/09 and for the reasons set-forth below.

Hoon et al teaches a method of detecting circulating melanoma cells comprising: (a) isolating nucleic acid from a sentinel lymph node (SLN) sample, tumor draining lymph node sample, or blood sample obtained from a melanoma patient; (b) amplifying mRNA transcripts encoded by GalNAcT, MAGE-3, and MART-1 marker genes from the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient wherein amplification is done by PCR; (c) detecting the levels of GalNAcT, MAGE-3, and MART-1 mRNA transcripts in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the melanoma patient; and (d) comparing levels of the mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in nucleic acid from a SLN, tumor draining lymph node sample, or blood sample obtained from a second melanoma patient to levels of mRNA transcripts encoded by the GalNAcT, MAGE-3, and MART-1 marker genes in the nucleic acid from the SLN sample, tumor draining lymph node sample, or blood sample obtained from the first melanoma patient to determine melanoma status (see lines 15-19 of column 3, claim 69, and lines 57-59 of column 41, in particular), assigning a clinical melanoma stage to the subject (column 38 lines 45-51 and column 40 lines 4-6, in particular), predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). It is noted that "MAGE-3" is an alternate name of "MAGE-A3" as recited in the instant claims. The method taught by Hoon et al further comprises predicting melanoma recurrence or survival of the subject for a period of

greater than 30 months following removal of a primary tumor, SLND, or both (Figure 1, in particular). The method taught by Hoon et al further comprises samples wherein the histopathology of the body fluid or tissue sample is determined by H&E and would determine whether the SLN or blood sample from the subject is histopathologically positive of negative for melanoma cells (Example VII, in particular). Hoon et al further teaches a method wherein a high number of genes expressed indicates an advanced melanoma stage, progression or melanoma, a high probability of melanoma recurrence, or a low probability of survival (Figure 1, in particular). Hoon et al further teaches a method wherein the samples are frozen (see Example VII, in particular). In the method of Hoon et al, the detection of GalNac-T, MAGE-3, and MART-1 in a sample from a subject, as compared to a subject without detected GalNac-T, MAGE-3, and MART-1, "upstages" a prognosis and correlates with melanoma recurrence and shorter relapse-free survival because detection indicates the presence of circulating melanoma cells. Further, the abstract of Hoon et al states "Methods using multiple markers provide increased sensitivity over existing methods" and Example XIII of Hoon et al states "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, subjects expressing a higher number of melanoma-specific markers (such as GalNac-T, MAGE-3, and MART-1) in samples would be expected to be worse off than patients expressing a lower number of melanoma-specific markers because those expressing a lower number of melanoma-specific markers would include

those that express no markers, as well as false-positive results, and subjects with a higher number of detected (above zero copy number) melanoma-specific markers would more accurately detect circulating melanoma cells in subjects that have a higher likelihood of recurrence and shorter relapse-free survival as compared to patients expressing a lower number of detected (above zero copy number) melanoma-specific markers which do not have circulating melanoma cells.

Hoon et al does not specifically teach PAX-3 being part of the panel of genes used. However, this deficiency is rendered obvious or made up in the teachings of Scholl et al.

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX-3 and MAGE-A3, and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting and characterizing metastatic melanoma as taught by Hoon et al with a panel of genes comprising PAX-3 because Hoon et al teaches incorporating nucleic acids of any melanoma markers into the panel (see column 3 line 9-14, in particular) and Scholl et al teaches PAX-3 nucleic acid is a melanoma marker (see Table 1 and Table 2 of Scholl et al, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when performing the method taught by Hoon et al with a panel

of genes comprising PAX-3 because Scholl et al has demonstrated that PAX-3 nucleic acid is a marker of metastatic melanoma (see Table 1 and Table 2 of Scholl et al, in particular). Further, Scholl et al teaches PAX-3 and MAGE-A3 are overexpressed in metastatic malignant melanoma cells in vivo (pages 825-826, in particular) and Hoon et al teaches GalNAc-T, MAGE-A3 (MAGE-3), and MART-1 are also overexpressed in metastatic melanoma cells in vivo (column 2 line 53 to column 3 line 36, lines 15-20 of column 3, and Example IV, in particular). Since Scholl et al and Hoon et al teach overlapping panels of genes that are overexpressed in the same type of sample (metastatic melanoma cells) and Hoon et al teaches metastatic melanoma cells would be detected in body fluid samples (column 2 line 53 to column 3 line 36 and Example IV, in particular), one of skill in the art would expect PAX-3 to be overexpressed by metastatic melanoma cells in body fluid comprising metastatic melanoma cells. Further, one of skill would expect said melanoma recurrence and survival would be predicted for a period of at least three years following removal of a primary tumor, SLND, or both by detecting GalNAc-T, MAGE-A3, and MART-1 because Hoon et al teaches said melanoma recurrence and survival would be predicted for a period of at least 30 months following removal of a primary tumor, SLND, or both by detecting multiple markers of circulating melanoma cells including MAGE-A3 (Figure 1, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 3/23/10, Applicant cites the declaration of German Pihan and argues that Scholl et al does not disclose a method of detecting metastatic melanoma

using PAX3. Applicant further states that Scholl et al does not disclose that PAX3 is useful for detecting melanoma in histopathologically negative sentinel lymph nodes nor in a body fluid as claimed. Applicant further cites the declaration of German Pihan and argues that one of skill in the art would not interpret the teachings of Scholl et al as suggesting that detection of PAX3 in histopathologically negative lymph nodes would be a functional test for occult melanoma metastasis. Applicant further argues that Scholl et al does not perform any detection of occult disease and that only a fraction of tissue samples with histopathologically evident metastatic melanoma expressed PAX3 mRNA. Applicant further states that occult tumors will not have the same mRNA expression patterns as overt metastasis and that the data of Scholl et al would not provide the impetus for one of skill in the art to believe that PAX3 would be useful in detecting occult metastases in histopathologically negative lymph nodes. Applicant further states that the experiments described in Scholl et al are directed to detection of PAX3 in samples known to contain melanoma cells wherein the samples are melanoma cell lines, cultured melanoma cells, and overt tumors for patients at various stages of disease. Applicant further argues that it is impossible to assess a rate of false positive results because Scholl et al does not present any experimental results for samples not containing melanoma. Applicant argues that expression studies with melanoma cell lines and cultured melanoma cells are not predictive of expression of in vivo cancer cells. Applicant further argues that the claimed invention provides unexpected results of having a reduced incidence of false positive results. Applicant further argues that the prior art is replete with articles showing many combinations of markers are of marginal

or no clinical utility or have no advantage over a single marker. Applicant further argues that multi-marker melanoma analysis was not established at the filing date of the instant application. Applicant further argues that the Office Action fails to mention sections of Hoon et al regarding detecting multiple markers are directed to breast cancer. Applicant further states that teachings directed to sensitivity in breast cancer do not predict behavior in melanoma. Applicant further cites Scoggins et al (Journal of Clinical Oncology, 2006, 24(18): 2849-2857) and argues that the utility of melanoma markers was still uncertain a number of years after filing the present invention. Applicant further argues that the simultaneous expression of two markers selected from tyrosinase, MART1, MAGE3, and GP-100 was not associated with any longer overall survival than one or no marker expression. Applicant further cites Mocellin et al (TRENDS in Molecular Medicine, 2003, 9(5):189-195) and states that the Examiner fails to appreciate the role that qRT-PCR played in cancer research prior to filing of the present patent application. Applicant further argues that the Mocellin et al article eviscerates the Examiner's contention that quantification of cancer related markers can be correlated with prognosis. Applicant further cites Tsao et al (ARCH DERMATOL, 2001, 137:325-330), and argues that the Examiner's assertion that more markers are better is undercut by a confused state of the art circa 2002. Applicant further states that the utility of qRT-PCR and quantification of mRNA in general was unproven at the time. Applicant further cites Gerber et al (Journal of Clinical Oncology, 2001, 19(4): 960-971), which Applicant states casts considerable doubt on the recognized utility of qRT-PCR in providing a prognostic value circa 2001. Applicant further cites Hilari et al (Ann Surg Oncol, 2009,

16(1): 177-185) and argues that prediction of disease outcome is useless unless a comparison to known prognostic factors for the tumor in question is performed in a multivariate statistical analysis as set-forth in the present application. Applicant further cites Tatilidil et al (Modern Pathology, 2007, 20: 427-434), and argues that Tatlidil et al demonstrates that tyrosinase markers are of no prognostic value. Applicant further cites Denninghoff et al (Mol Diag, 2004, 8(4): Abstract), and argues that RT-PCR of a single marker is of minimal prognostic value. Applicant further argues that Scoggins, Mocellin, Tsao, Gerber and more recent articles indicate that the relevancy of gene markers in cancer diagnosis was uncertain at the time the present application was filed and that the references demonstrate that not just any combination of cancer related gene markers would be useful for determining a melanoma patient's prognosis. Applicant further argues that the prior art exemplifies a situation wherein there are a number of possible choices without an indication of which parameters are critical. Applicant further states that blanket conclusions regarding types of cancers, cancer gene markers, expression levels of such gene markers, and the correlation of prognosis are not obvious. Applicant further states that uncertainty is realized in Mocellin et al, which states that “although the clinical utility of PCR-based MRD evaluation for hematological malignancies is well established, the experience with solid tumors is more limited". Applicant further argues that conclusions regarding hematological cancers cannot be imputed to solid tumors.

The amendments to the claims and the arguments found in the Reply of 3/23/10 have been carefully considered, but are not deemed persuasive. In regards to the argument that Scholl et al does not disclose a methods of detecting metastatic

melanoma using PAX3, Scholl et al discloses method of detecting metastatic melanoma using PAX3 (see Figure 2E, where “PAX3 expression was confined to malignant metastasis and not observed in surrounding normal tissue”, and page 825, in particular). Further, see the following passage from page 825: "Hence, the expression of PAX3 is restricted to malignant melanomas already at early stage I as well as their distant metastases and not detected in normal skin melanocytes or benign lesions".

In regard to the arguments that Scholl et al does not disclose that PAX3 is useful for detecting melanoma in histopathologically negative sentinel lymph nodes nor in a body fluid as claimed, that one of skill in the art would not interpret the teachings of Scholl et al as suggesting that detection of PAX3 in histopathologically negative lymph nodes would be a functional test for occult melanoma metastasis and that Scholl et al does not perform any detection of occult disease: Hoon et al discloses that metastatic melanoma cells are to be detected in sentinel lymph nodes and body fluids (see lines 15-19 of column 3, claim 69, and lines 57-59 of column 41, in particular). The method taught by Hoon et al further comprises samples wherein the histopathology of the body fluid or tissue sample is determined by H&E and would determine whether the SLN or blood sample from the subject is histopathologically positive of negative for melanoma cells (Example VII, in particular). As a known marker for metastatic melanoma (see above discussion of Scholl et al), one of ordinary skill in the art at the time the invention was made would have been motivated to perform the method of detecting and characterizing metastatic melanoma as taught by Hoon et al with a panel of genes comprising PAX-3 because Hoon et al teaches incorporating nucleic acids of any

melanoma markers into the panel (see column 3 line 9-14, in particular) and Scholl et al teaches PAX-3 nucleic acid is a melanoma marker (see Table 1 and Table 2 of Scholl et al, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when performing the method taught by Hoon et al with a panel of genes comprising PAX-3 because Scholl et al has demonstrated that PAX-3 nucleic acid is a marker of metastatic melanoma (see Table 1 and Table 2 of Scholl et al, in particular). Further, Scholl et al teaches PAX-3 and MAGE-A3 are overexpressed in metastatic malignant melanoma cells in vivo (pages 825-826, in particular) and Hoon et al teaches GalNAc-T, MAGE-A3 (MAGE-3), and MART-1 are also overexpressed in metastatic melanoma cells in vivo (column 2 line 53 to column 3 line 36, lines 15-20 of column 3, and Example IV, in particular). Since Scholl et al and Hoon et al teach overlapping panels of genes that are overexpressed in the same type of sample (metastatic melanoma cells) and Hoon et al teaches metastatic melanoma cells would be detected in body fluid samples (column 2 line 53 to column 3 line 36 and Example IV, in particular), one of skill in the art would expect PAX-3 to be overexpressed by metastatic melanoma cells in body fluid comprising metastatic melanoma cells.

In regards to the statement that only a fraction of tissue samples with histopathologically evident metastatic melanoma expressed PAX3 mRNA, this is not surprising and provides clear motivation to use numerous markers of metastatic melanoma when detecting melanoma. This motivation is clearly stated in the abstract of Hoon et al, which states “Methods using multiple markers provide increased

sensitivity over existing methods". Heterogeneity of tumors, in general, is illustrated in the breast cancer data of Example XIII of Hoon et, which discloses: "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker".

In regards to the argument that occult tumors will not have the same mRNA expression patterns as overt metastasis and that the data of Scholl et al would not provide the impetus for one of skill in the art to believe that PAX3 would be useful in detecting occult metastases in histopathologically negative lymph nodes, known heterogeneity of tumors provides clear motivation to use numerous markers of metastatic melanoma when detecting melanoma. This motivation is clearly stated in the abstract of Hoon et al, which states "Methods using multiple markers provide increased sensitivity over existing methods". Heterogeneity of tumors, in general, is illustrated in the breast cancer data of Example XIII of Hoon et, which discloses: "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker".

In regards to the argument that it is impossible to assess a rate of false positive results because Scholl et al does not present any experimental results for samples not containing melanoma, the normal adjacent tissue of sample illustrated in Figure 2E of Scholl provides an excellent negative control. In Figure 2E of Scholl et al, "PAX3 expression was confined to malignant metastasis and not observed in surrounding

normal tissue" (see page 825, in particular). Further, see the following passage from page 825: "Hence, the expression of PAX3 is restricted to malignant melanomas already at early stage I as well as their distant metastases and not detected in normal skin melanocytes or benign lesions".

In regards to the assertion that expression studies with melanoma cells lines and cultured melanoma cells are not predictive of expression of in vivo cancer cells, Scholl et al teaches that "the in situ hybridization data correlates perfectly with the RT-PCR results of the cultured melanomas (Table 1)". However, this rejection is not based on the expression of PAX3 in melanoma cells lines and cultured melanoma cells. Rather, this rejection is based on expression of PAX3 in tumor tissue sections.

In regards to the argument that the claimed invention provides unexpected results of having a reduced incidence of false positive results, there is nothing unexpected about obtaining a reduced incidence of false positive results when using multiple biomarkers. A reduction in false positive is expected when using multiple biomarkers and is an obvious reason to use multiple biomarkers.

In regard to the arguments that the prior art is replete with articles showing many combinations of markers are of marginal or no clinical utility or have no advantage over a single marker and that multi-marker melanoma analysis was not established at the filing date of the instant application, the cited art teaches otherwise. Specifically, the abstract of Hoon et al, which states "Methods using multiple markers provide increased sensitivity over existing methods". Heterogeneity of tumors, in general, is illustrated in the breast cancer data of Example XIII of Hoon et, which discloses: "None of the

markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, Hoon et al (J Clin Oncol, 1995, 13(18): 2109-2116) teaches multi-marker analysis to detect occult circulating melanoma cells was established *well before* the filing date of the instant application (see right column of page 2114, in particular).

In regard to the arguments that the Office Action fails to mention sections of Hoon et al regarding detecting multiple markers are directed to breast cancer and that teachings directed to sensitivity in breast cancer do not predict behavior in melanoma, the abstract of Hoon et al states "Methods using multiple markers provide increased sensitivity over existing methods". Heterogeneity of tumors, in general, is illustrated in the breast cancer data of Example XIII of Hoon et, which discloses: "None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells. In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, Hoon et al clearly teaches multiple markers are to be used to detect metastatic melanoma (lines 15-20 of page 3, claim 1, and claim 5 of Hoon et al, in particular).

In regards to the citation of Scoggins et al and argument that the utility of melanoma markers was still uncertain a number of years after filing the present invention, the utility of PAX3, GalNac-T, MAGE-3, and MART-1 as melanoma markers was well known prior to filing the present invention (see above). It is further noted this is not a utility rejection. Further, Hoon et al (J Clin Oncol, 1995, 13(18): 2109-2116)

teaches multi-marker analysis to detect occult circulating melanoma cells was established *well before* the filing date of the instant application (see right column of page 2114, in particular).

In regards to the argument that the simultaneous expression of two markers selected from tyrosinase, MART1, MAGE3, and GP-100 was not associated with any longer overall survival than one or no marker expression, Scoggins et al teaches expression of more than one of tyrosinase, MART1, MAGE3, and GP-100 is associated worse disease free survival (DFS) and a worse distant-disease free survival (DDFS) (see page 2855, in particular).

In regards to the argument the citation of Mocellin et al, the statement that the Examiner fails to appreciate the role that qRT-PCR played in cancer research prior to filing of the present patent application, and that the Mocellin et al article eviscerates the Examiner's contention that quantification of cancer related markers can be correlated with prognosis: this rejection is not based on use of qRT-PCR. Arguments involving qRT-PCR are discussed below.

In regards to the citation of Tsao et al and argument that the Examiner's assertion that more markers are better is undercut by a confused state of the art circa 2002, the abstract of Hoon et al states “Methods using multiple markers provide increased sensitivity over existing methods”. Heterogeneity of tumors, in general, is illustrated in the breast cancer data of Example XIII of Hoon et, which discloses: “None of the markers alone would have been able to detect cancer cells in all of the specimens. This variation in marker detection reflects the heterogeneity of tumor cells.

In conclusion, multiple markers are more sensitive to detection of breast cancer than any one marker". Further, Hoon et al clearly teaches multiple markers are to be used to detect metastatic melanoma (lines 15-20 of page 3, claim 1, and claim 5 of Hoon et al, in particular). Further, Hoon et al (J Clin Oncol, 1995, 13(18): 2109-2116) teaches "the use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity to detect cell that express few or no copies of tyrosinase mRNA ... The number of markers detected in individual patients was significantly correlated with disease stage and progression. This suggests that there could be higher expression of individual marker genes, greater heterogeneity of tumor cells, or more tumor cells in circulation at advanced stages of disease" *well before* the filing date of the instant application (see right column of page 2114, in particular).

In regards to the argument that utility of qRT-PCR and quantification of mRNA in general was unproven at the time, this rejection is not based on use of qRT-PCR. Arguments involving qRT-PCR are discussed below.

In regards to the citation of Gerber et al, which Applicant states casts considerable doubt on the recognized utility of qRT-PCR in providing a prognostic value circa 2001, this rejection is not based on use of qRT-PCR. Arguments involving qRT-PCR are discussed below.

In regards to the citation of Hilari et al and argument that prediction of disease outcome is useless unless a comparison to known prognostic factors for the tumor in question is performed in a multivariate statistical analysis as set-forth in the present application, this is not a utility rejection. Further, Hoon et al teaches methods of

predicting recurrence (Figure 1 and column 38 lines 60-65, in particular), predicting survival of the subject (Figure 1, in particular), and monitoring melanoma progression or treatment response (column 21 lines 41-60 and column 14 lines 41-59, in particular). Further, subjects expressing a higher number of melanoma-specific markers (such as GalNac-T, MAGE-3, and MART-1) in samples would be expected to be worse off than patients expressing a lower number of melanoma-specific markers because those expressing a lower number of melanoma-specific markers would include those that express no markers, as well as false-positive results, and subjects with a higher number of melanoma-specific markers would more accurately detect circulating melanoma cells in subjects that have a higher likelihood of recurrence and shorter relapse-free survival as compared to patients expressing a lower number of melanoma-specific markers which do not have circulating melanoma cells.

In regards to the argument the citation of Tatilidil et al and argument that Tatlidil et al demonstrates that tyrosinase markers are of no prognostic value, Tatlidil teaches that their findings are limited by a short duration of follow-up (see left column of page 433, in particular). Further, the cited references teach the use of multiple markers of metastatic melanoma (not just tyrosinase).

In regards to the citation of Denninghoff et al and argument that RT-PCR of a single marker is of minimal prognostic value, the cited references teach the use of multiple markers of metastatic melanoma (not just tyrosinase). Further, Denninghoff et al does not teach that RT-PCR of a single marker is of minimal prognostic value.

In regard to the arguments that Scoggins, Mocellin, Tsao, Gerber and more recent articles indicate that the relevancy of gene markers in cancer diagnosis was uncertain at the time the present application was filed, that the references demonstrate that not just any combination of cancer related gene markers would be useful for determining a melanoma patient's prognosis and that the prior art exemplifies a situation wherein there are a number of possible choices without an indication of which parameters are critical, and that blanket conclusions regarding types of cancers, cancer gene markers, expression levels of such gene markers, and the correlation of prognosis are not obvious: the relevancy of PAX3, GalNac-T, MAGE-3, and MART-1 as melanoma markers and determining prognosis based on expression levels of such markers to determine prognosis were well known prior to filing the present invention (see above).

In regard to the argument that uncertainty is realized in Mocellin et al, which states that “although the clinical utility of PCR-based MRD evaluation for hematological malignancies is well established, the experience with solid tumors is more limited" and conclusions regarding hematological cancers cannot be imputed to solid tumors, Mocellin et al teaches qRT-PCR has been used to detect circulating melanomas (see right column of page 192, in particular). Mocellin et al further teaches "whereas histopathological examination of sentinel nodes is time-consuming and might miss microscopic disease made of few malignant cells, qrt-PCR potentially offers a rapid way to identify and quantify sentinel node micrometastasis” (see right column of page 192, in particular). Therefore, Mocellin et al provides clear motivation to use qrt-PCR to detect

micometastasis of melanoma cells in sentinel nodes. Further, Mocellin et al stresses the aspect of heterogeneity of solid tumor types (see right column of page 192, in particular), providing more motivation to use multiple markers when detecting solid tumor types.

Claims 1-5, 7, 10, 34-38 and 40 remain rejected and newly added claims 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al (US Patent 6,057,105; 5/2/00) in view of Scholl et al (2/01, Cancer Research, 61:823-826) as applied to claims 1-3, 5, 7, 10, 34-36, 38, and 40 above, and further in view of Johansson et al (2000, Clinical Chemistry, 46(7): 921-927) for the reasons stated in the Office Action of 11/4/09 and for the reasons set-forth below.

Teaching of claims 1-3, 5, 7, 10, 34-36, 38, and 40 by Hoon et al in view of Scholl et al is discussed above.

The combined teachings of Hoon et al and Scholl et al do no specifically teach using qRT-PCR to detect PAX3, MAGE-A3, and GalNacT expression. However, these deficiencies are made up in the teachings of Johansson et al.

Johansson et al teaches a reproducible method comprising performing qRT to quantitatively detect copy number of mRNA markers of melanoma in blood samples (pages 922-923, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use qRT to detect expression of marker genes when performing the method of detecting and characterizing metastatic melanoma as taught by the

combined teachings of Hoon et al and Scholl et al because qRT is a quantitative method of detecting specific mRNA transcripts (Figure 4 of Johansson et al, in particular) which would streamline the method and facilitate comparison between multiple experiments and remove discrepancies relying on visual inspection of an electrophoresis gel (see Hoon et al at lines 13-14 of column 17, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success when using qRT to detect expression of marker genes when performing the method taught by the combined teachings of Hoon et al and Scholl et al because Johansson et al demonstrates that qRT quantitatively detects transcripts which are mRNA markers of melanoma in body fluid samples (pages 922-923, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 3/23/10, Applicant argues that Johansson does not cure alleged deficiencies of Hoon et al in view of Scholl et al. Such arguments have been addressed above.

In regards to the citation of Mocellin et al, statement that the Examiner fails to appreciate the role that qRT-PCR played in cancer research prior to filing of the present patent application, and argument that the Mocellin et al article eviscerates the Examiner's contention that quantification of cancer related markers can be correlated with prognosis: Mocellin et al teaches qRT-PCR is “a powerful ally in cancer research” (see title, in particular). Mocellin et al further teaches qRT-PCR has been used to detect circulating melanomas (see right column of page 192, in particular). Mocellin et al

further teaches "whereas histopathological examination of sentinel nodes is time-consuming and might miss microscopic disease made of few malignant cells, qrt-PCR potentially offers a rapid way to identify and quantify sentinel node micrometastasis" (see right column of page 192, in particular). Therefore, Mocellin et al provides clear motivation to use qrt-PCR to detect micometastasis of melanoma cells in sentinel nodes. Further, Mocellin et al stresses the aspect of heterogeneity of solid tumor types (see right column of page 192, in particular), providing more motivation to use multiple markers when detecting solid tumor types.

In regards to the citation of Tsao et al and statement that the utility of qRT-PCR and quantification of mRNA in general was unproven at the time, this is not a utility rejection. Further, Johansson et al teaches a reproducible (provable) method comprising performing qRT to quantitatively detect mRNA markers of melanoma in blood samples (pages 922-923, in particular).

In regards to the citation of Gerber et al, which Applicant states casts considerable doubt on the recognized utility of qRT-PCR in providing a prognostic value circa 2001: Johansson et al teaches a reproducible (provable) method comprising performing qRT to quantitatively detect mRNA markers of melanoma in blood samples (pages 922-923, in particular). Further, the CK-19 marker, determined by Gerber et al to have no diagnostic value as an mRNA marker for micrometastasis, is not a marker of the cited references.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Sean E Aeder/
Primary Examiner, Art Unit 1642